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NEW DELHI - 110 008.

I, the undersigned, being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.* ***234/Del/03*** *dated* ***6th March 2003.***

Witness my hand this 7th Day of October 2003.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

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0254 DEL 03

FORM 1

06 MAR 2003

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED,** a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A METHOD FOR PREPARATION OF CONTROLLED RELEASE MULTIPLE UNIT SYSTEM OF GLIPIZIDE"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. SANKAR RAMAKRISHNAN

b. RAJEEV SINGH RAGHUVANSHI

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

DUPLICATE

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana), INDIA.
Tel. No. (91-124) 2343126; 2342001 – 10; 5012501-10
Fax No. (91-124) 2342027

6. Following declaration was given by the inventors in the convention country:

We, SANKAR RAMAKRISHNAN, RAJEEV SINGH RAGHUVANSHI of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representative.

a. (SANKAR RAMAKRISHNAN)

b. (RAJEEV SINGH RAGHUVANSHI)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. 687968 dated 18/2/2003 on Axis Grindlays

We request that a patent may be granted to us for the said invention.

Dated this 5TH day of **MARCH,** 2003.

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
COMPANY SECRETARY

FORM 2 0234 DEL 03

The Patents Act, 1970
(39 of 1970)

06 MAR 2003

COMPLETE SPECIFICATION

(See Section 10)

A METHOD FOR PREPARATION OF CONTROLLED RELEASE MULTIPLE UNIT SYSTEM OF GLIPIZIDE

DUPLICATE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019
A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

This invention relates to a method for preparation of controlled release multiple unit system of glipizide.

Glipizide is an oral blood glucose-lowering drug and is indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with non-insulin dependent diabetes mellitus. It stimulates secretion of insulin from the beta cells of pancreatic islet tissue and also exhibits extra-pancreatic action such as the ability to increase the number of insulin receptors.

Chemically, glipizide is N-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl] ethyl]-5-methylpyrazine carboxamide. Glipizide is a white, odorless powder with a pKa of 5.9, and is insoluble in both water and alcohol. These physicochemical properties of glipizide demand special techniques to formulate a dosage form that can administer the drug at a controlled and predetermined rate.

Presently, extended release oral tablets of glipizide are marketed by Pfizer under the trade name Glucotrol® XL. It is an osmotic drug delivery device based on the push pull technology. The delivery device comprises a bi-layered core tablet coated with a semipermeable membrane having an orifice drilled on the coat for release of glipizide. The bilayered core tablet consists of a glipizde layer and a push layer comprising of swellable polymers. When placed in dissolution media or gastrointestinal fluid the device absorbs water through the semipermeable membrane, which leads to swelling of polymers in the push layer. This exerts a physical force on the drug layer forcing it out of the device through the orifice.

Fabrication of such an osmotic drug delivery device is a highly complicated process, involving multiple compression, skillful coating and drilling steps. The selection and optimization of ingredients for this system too is lengthy and troublesome. Further, the performance of the device is highly dependent upon the osmotic pressure of fluids in the gastrointestinal tract. Other drawbacks include dose dumping caused by intentional or accidental breakdown of the delivery device; and variable gastric emptying of the delivery device, incomplete drug release under high gastrointestinal tract motility conditions, depending on the presence or absence as well as the type of food taken by the patient.

In the light of above, there exists a pressing need for the development of a controlled release formulation of glipizide for oral administration, which is devoid of above limitations. We have surprisingly discovered that these limitations can be overcome with the use of multiple unit system, wherein each individual unit is formulated with controlled release characteristics. These individual units are finally compressed into tablet or filled as such into capsule/sachet. When administered, the individual units are dispersed freely into the gastrointestinal contents and due to the smaller size of dispersed units, performance of the dosage form is independent of inter and intra patient variability in gastric emptying time. This technology has an added advantage of division of doses without formulation and process changes.

Hence, one embodiment provides a method for preparation of controlled release multiple unit system of glipizide prepared by coating inert core with glipizide and rate controlling polymer

Another embodiment provides a method for preparation of controlled release multiple unit system of glipizide prepared by coating glipizide containing core with rate controlling polymer.

The multiple unit system of the present invention may contain an inert core; or a glipizide containing core, wherein glipizide is incorporated within the core.

The controlled release multiple unit system may be prepared by:

a. Coating inert core with glipizide and rate controlling polymer, or with glipizide and rate controlling polymer layer separately; optionally applying an inert coat between inert core and glipizide layer, between glipizide layer and rate controlling polymer layer, or over rate controlling polymer layer.

b. Coating glipizide containing core with rate controlling polymer; optionally applying an inert coat between glipizide containing core and rate controlling polymer layer, or over rate controlling polymer layer.

The core may be of any geometric shape though spheres are preferred for the ease of uniform coating. The core diameter may vary from about 100 to 1200 µm.

The controlled release multiple units prepared from any of the above processes may optionally be coated with an immediate release layer of glipizide and/or an outermost non-functional waxy layer. The waxy layer helps in imparting elasticity and compressibility to the units, thereby aiding compression of units into tablet or filling into capsule/sachet without altering the dissolution profile and hence the bioavailability and clinical effects.

Methods of manufacturing the inert core or glipizide containing core include:

a. Extrusion-Spheronization: The inert core material with or without glipizide and other pharmaceutical excipients is granulated by addition of a binder solution/dispersion. The wet mass is passed through an extruder equipped with a screen. The extrudates are spheronized in a spheronizer. The resulting spheroids/pellets are dried and sieved for further applications.

b. Granulation: The inert core material with or without glipizide and other pharmaceutical excipients is dry-mixed and then the mixture is wetted by addition of a binder solution/dispersion in a high shear-granulator/mixer. The granules are kneaded after wetting by the combined actions of mixing and milling. The resulting granules or pellets are dried and sieved for further applications.

Alternatively, glipizide-containing cores can also be prepared by replacing inert core material with glipizide in the above two methods of preparing inert cores.

Alternatively, the inert core may also be a commercially available product.

The inert core material of the present invention may be selected from pharmaceutically inert insoluble, soluble or swellable material. The insoluble inert cores are composed of sand (silicon dioxide), glass, microcrystalline cellulose (celphere) or plastic (polystyrene) material. On the other hand soluble inert cores are composed of sugar selected from glucose, mannitol, lactose, xylitol, dextrose, sucrose and the like. The swellable inert cores are composed of hydroxypropyl methylcellulose.

Commercially available inert core is selected from sugar sphere, non pareil seed, celphere and the like.

Glipizide, polymer, or optional layers can be applied to the core as solution/dispersion using any conventional coating technique known in the prior art such as spray coating in a conventional coating pan or fluidized bed processor; or dip coating. Alternatively, coating can also be performed using hot melt technique whenever possible.

The solvents used for making a solution/dispersion of the coating material for the purpose of present invention may be selected from methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and mixtures thereof.

The glipizide layer of the present invention comprises glipizide with or without other pharmaceutically inert excipients. Optionally this layer may also contain buffering agents. Buffers help in maintaining the pH of the glipizide layer and/or local environment surrounding the controlled release particles above 7 thereby aid in dissolution of glipizide in the dissolution media/gastrointestinal fluids. It may be applied as aqueous/non-aqueous solution or dispersion of drug in water/organic solvent or mixtures thereof.

Buffering agents of the present invention may be selected from dibasic sodium phosphate, sodium ascorbate, meglumine, sodium citrate trimethanolamine, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonia, tertiary sodium phosphate, diethanolamine, ethylenediamine, L-lysine and mixtures thereof.

The rate controlling polymer layer of the present invention comprises one or more polymers with or without other pharmaceutically inert excipients. Alternatively, a single layer may contain drug and rate controlling polymers. This layer may be applied as aqueous/non aqueous solution/dispersion of polymers in water/organic solvent. The polymers of the rate controlling polymer layer may be selected from cellulosic polymers, waxes, methacrylic acid polymers and mixtures thereof.

Cellulosic polymers of the present invention may be selected from ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, cellulose acetate, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate and the like.

Methacrylic acid polymers of the present invention may be selected from those commercially available as Eudragit ® RL and RS and the like.

The inert coat of the present invention may be composed of polymers selected from hydroxypropyl methylcellulose, polyvinyl pyrrolidone, methacrylic acid copolymers and the like, with or without other pharmaceutically inert excipients.

The waxy material of the present invention may be selected from the range of polyethylene glycols (PEGs) of various molecular weights. PEGs may be selected from PEG 600, PEG 4000, PEG 6000, PEG 8000, PEG 20000 and the like. Optionally, this layer may also contain other pharmaceutically inert excipients. The amount of the waxy material may vary from about 1 % to about 100 % by weight of the weight of individual unit.

The modified release units prepared by any of the above methods can be mixed with other pharmaceutically inert excipients (if required) and compressed into tablet or filled into capsule/sachet using techniques known in the art for these purposes. The final tablet or capsule may optionally be coated, if desired.

The pharmaceutically inert excipients as used herein include surfactants, binders, diluents, disintegrants, lubricants, glidants, plasticizers, stabilizers and coloring agents.

Surfactants of the present invention may be selected from both non-ionic and ionic (Cationic, Anionic and Zwitterionic) surfactants suitable for use in pharmaceutical compositions. These include polyethoxylated fatty acids and its derivatives, for example polyethylene glycol 400 distearate, polyethylene glycol – 20 dioleate, polyethylene glycol 4 –150 mono dilaurate, polyethylene glycol –20 glyceryl stearate; alcohol – oil transesterification products, for example polyethylene glycol – 6 corn oil;

polyglycerized fatty acids, for example polyglyceryl – 6 pentaoleate; propylene glycol fatty acid esters, for example propylene glycol monocaprylate; mono and diglycerides for example glyceryl ricinoleate; sterol and sterol derivatives; sorbitan fatty acid esters and its derivatives, for example polyethylene glycol – 20 sorbitan monooleate, sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol; sugar esters, for example sucrose monopalmitate; polyoxyethylene – polyoxypropylene block copolymers known as "poloxamer"; ionic surfactants, for example sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, palmitoyl carnitine; and the like.

Binders of the present invention may be selected from methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and the like.

Diluents of the present invention may be selected from calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose-microcrystalline, cellulose powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners and mixtures thereof.
Lubricants and glidants of the present invention may be selected from colloidal anhydrous silica, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax and the like.

Plasticizers of the present invention may be selected from polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate, dibutyl sebacate and the like.

Stabilizers of the present invention may be selected from antioxidants, buffers, acids and the like.

The coloring agents of the present invention may be selected from any FDA approved colors for oral use.

The invention is further illustrated by the following examples but they should not be construed as limiting the scope of the invention in any way.

EXAMPLE 1

Controlled release multiple units:

(i) Inert core	
Celphere	148 mg
(ii) Drug layer	
Glipizide	10 mg
Polyethylene glycol	4.7 mg
Hydroxypropyl methylcellulose	1.7 mg
Polyvinyl pyrrolidone	3.0 mg
Tween 80	0.5 mg
Lactose	3.0 mg
iii) Rate controlling layer	
Ethyl cellulose	10 mg
Hydroxypropyl methylcellulose	5 mg
Triacetin	1.7 mg
Talc	0.5 mg

Procedure:

1. Polyethylene glycol, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, tween and lactose were dissolved in water and glipizide was then dispersed in the above solution.
2. Celpheres were loaded in Glatt and coated with drug dispersion of step 1.
3. A solution of ethyl cellulose, hydroxypropyl methylcellulose and triacetin was prepared in a mixture of methylene chloride and isopropyl alcohol into which talc was dispersed.
4. Drug loaded pellets of step 2 were then coated with dispersion of step 3 using a Glatt to prepare controlled release multiple units.

Table 1 illustrates the comparative release patterns *in vitro* for controlled release multiple units prepared according to example 1.

Table 1. *In vitro* release pattern of controlled release multiple units using USP apparatus – II, at 50 rpm and pH 7.5

Time (Hours)	Cumulative percentage release of glipizide from controlled release multiple units
1	10
2	18
4	29
8	46
12	62
16	74
20	89
24	98

EXAMPLE 2

Controlled release multiple units:

(i) Inert core

Celphere	148 mg

(ii) Drug layer

Glipizide	10.0 mg
Polyethylene glycol	4.7 mg
Hydroxypropyl methylcellulose	1.7 mg
Polyvinyl pyrrolidone	3.0 mg
Tween 80	0.5 mg
Lactose	3.0 mg

iii) Rate controlling layer

Ethyl cellulose	4.6 mg
Hydroxypropyl methylcellulose	2.9 mg
Triacetin	0.8 mg
Talc	0.3 mg

Procedure:

1. Polyethylene glycol, hydroxypropyl methylcellulose, polyvinyl pyrrolidone, lactose and tween were dissolved in water and glipizide was then dispersed in the above solution.
2. Celpheres were loaded in Glatt and coated with drug dispersion of step 1.
3. A solution of ethyl cellulose, hydroxypropyl methylcellulose and triacetin was prepared in a mixture of methylene chloride and isopropyl alcohol into which talc was dispersed.
4. Drug loaded pellets of step 2 were then coated with dispersion of step 3 using a Glatt to prepare controlled release multiple units.

Table 2 illustrates the comparative release patterns *in vitro* for controlled release multiple units prepared according to example 2.

Table 2. *In vitro* release pattern for controlled release multiple units using USP apparatus – II, at 50 rpm and pH 7.5

Time (Hours)	Cumulative percentage release of glipizide from controlled release multiple units
1	26
2	37
4	55
8	74
12	86
16	93
20	97
24	98

We Claim:

1. A method for preparation of controlled release multiple unit system of glipizide prepared by coating inert core with glipizide and rate controlling polymer.
2. A method for preparation of controlled release multiple unit system of glipizide prepared by coating glipizide containing core with rate controlling polymer.
3. The method according to claim 1 wherein glipizide and rate controlling polymer are present in the same layer.
4. The method according to claim 1 wherein glipizide and rate controlling polymer are present in separate layers.
5. The method according to claim 1, 2, 3 or 4 wherein controlled release multiple unit is coated with an immediate release layer of glipizide.
6. The method according to claim 3 or 4 wherein there is an inert coat between inert core and glipizide layer.
7. The method according to claim 4 or 6 wherein there is an inert coat between glipizide layer and rate controlling polymer layer.
8. The method according to claim 2 wherein there is an inert coat between glipizide containing core and rate controlling polymer layer.
9. The method according to claim 3, 4, 6, 7 or 8 wherein there is an inert coat over rate controlling polymer layer.
10. The method according to any of the preceding claims wherein controlled release multiple unit is coated with an outermost non functional waxy layer.
11. The method according to claim 1 or 2 wherein multiple unit system is compressed into tablet or filled into capsule/sachet.
12. The method according to claim 1or 2 wherein core is prepared by the method of extrusion-spheronization.
13. The method according to claim 1 or 2 wherein core is prepared by the method of granulation.
14. The method according to claim 1 wherein inert core is a commercially available product.
15. The method according to claim 14 wherein commercially available product is selected from sugar sphere, non pareil seed, celphere and the like.
16. The method according to claim 15 wherein inert core is celphere.
17. The method according to claim 1 wherein inert core is prepared from an inert core material.

18. The method according to claim 17 wherein inert core material may be selected from insoluble, soluble or swellable material.
19. The method according to claim 18 wherein inert core is prepared from an insoluble material.
20. The method according to claim 19 wherein insoluble material is sand (silicon dioxide), glass, microcrystalline cellulose or plastic(polystyrene).
21. The method according to claim 18 wherein inert core is prepared from a soluble material.
22. The method according to claim 21 wherein soluble material is a sugar selected from glucose, mannitol, lactose, xylitol, sucrose, dextrose and the like.
23. The method according to claim 18 wherein inert core is prepared from a swellable material.
24. The method according to claim 23 wherein swellable material is hydroxypropyl methylcellulose.

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25. The method according to claim 1 or 2 wherein the glipizide layer further contains buffering agent.
26. The method according to claim 25 wherein buffering agent is selected from dibasic sodium phosphate, sodium ascorbate, meglumine, sodium citrate trimetholamine, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, ammonia, tertiary sodium phosphate, diethanolamine, ethylenediamine, L-lysine and mixtures thereof.
27. The method according to claim 1or 2 wherein the release rate controlling polymers are selected from cellulosic polymers, methacrylic acid polymers, waxes and mixtures thereof.
28. The method according to claim 27 wherein cellulosic polymers include ethylcellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose, methylcellulose, carboxymethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, cellulose acetate, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate and the like.
29. The method according to claim 6, 7, 8 or 9 wherein inert coat is composed of polymers selected from hydroxypropyl methylcellulose, polyvinyl pyrrolidone, methacrylic acid copolymers and the like.

30. The method according to claim 10 wherein waxy layer is composed of polyethylene glycol.
31. The method according to claim 30 wherein polyethylene glycol (PEG) is selected from PEG 600, PEG 4000, PEG 6000, PEG 8000, PEG 20000 and the like.
32. The method according to claim 31 wherein polyethylene glycol is PEG 6000.
33. The method according to claim 1–10 wherein coating is applied as a solution/ dispersion.
34. The method according to claim 33 wherein solution/dispersion is prepared in solvents selected from methylene chloride, isopropyl alcohol, acetone, methanol, ethanol, water and mixtures thereof.
35. The method according to claim 1–10 wherein coating is applied using hot melt technique.
36. A method for preparing controlled release multiple unit system of glipizide for oral administration as described and illustrated by the examples herein.

Dated this **5TH** day of **March, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

ABSTRACT

A method for preparation of controlled release multiple unit system of glipizide is disclosed. Individual units comprising glipizide are coated with controlled release layer and optionally with inert and non functional waxy layers.

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